## REMARKS

The above-identified patent application is directed to a composition comprising a deglycosylated kringle 1-3 region fragment of a plasminogen protein. Claims 1-4, 6-12, 15, 16 and 27 were pending. In this Amendment and Response, applicants amend Claims 1 and 10-12 and add new Claims 29-38. Amendments and new claims do not introduce any new matter. Applicants amend Claim 1 to delete the language rejected by the Examiner. Claims 1-12 are amended to correct their dependency. New Claims 29-38 are based on Claims 1-4, 6-9, and 15-16 as pending prior to the present amendment. Reexamination and reconsideration of the application are requested in view of the amendments and the following remarks.

*Claim Rejections under 35 U.S.C. §112, first paragraph*

The Examiner rejects Claims 1-4, 6-12, 15 and 16 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

The Examiner asserts that the specification does not enable the *in vivo* or *in vitro* implementation of the claimed composition comprising a deglycosylated kringle 1-3 region fragment of a plasminogen protein. The Examiner states that the experimental evidence provided in the specification, particularly in Example 3, does not support applicants' claimed invention. Applicants disagree.

Applicants respectfully assert that the specification enables one of ordinary skill in the art to make and use the invention, as claimed. The specification teaches one of ordinary skill in the art how to make deglycosylated kringle-1-3 region fragments of plasminogen and provides experimental data that a deglycosylated kringle 1-3 fragment of plasminogen is a more efficient inhibitor of endothelial cell proliferation than a glycosylated kringle 1-3 fragment of plasminogen. The relative antiangiogenic properties of the deglycosylated and glycosylated kringle 1-3 fragments were assessed in an *in vitro*

endothelial cell proliferation assay. Thus, the specification provides direct *in vitro* experimental evidence that applicants' claimed composition is an effective inhibitor of endothelial cell proliferation.

Relying on the publication by Cao *et al.* (*Curr. Med. Chem. – Anti-Cancer Agents*, 2(6); 667-681, 2002; hereinafter "*Cao*"), the Examiner asserts: (1) that *in vitro* data have not been directly translated into antiangiogenic activity *in vivo*; (2) that k 1-3 may have a relatively short half-life *in vivo*; (3) and that antiangiogenic effects of a compound must be tested *in vivo*. The Examiner concludes that it would require undue experimentation from a skilled artisan to practice the invention, as claimed.

Applicants respectfully assert that undue experimentation is not required from one of ordinary skill in the art to make and use the claimed invention. Applicants respectfully bring to the Examiner's attention that an *in vitro* **or** *in vivo* model is acceptable for patentability purposes when there is a reasonable correlation with the condition; a rigorous or an invariable correlation is not required. MPEP 2164.02; *In re Brana,* 51 F.3d 1560, 1566 (Fed. Cir. 1995); *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985).

Applicants' claimed invention is a novel antiangiogenic composition comprising deglycosylated kringle 1-3 region fragments of plasminogen. Applicants obtained novel compositions comprising deglycosylated kringle 1-3 fragments of plasminogen and made a surprising discovery is that "deglycosylated fragments of the kringle 1-3 region of plasminogen are dramatically more antiangiogenic than glycosylated fragments of the kringle 1-3 region fragments of plasminogen."

In the specification, applicants describe testing antiangiogenic properties of a novel composition comprising deglycosylated kringle 1-3 region fragments of plasminogen relative to a compound with known antiangiogenic properties, namely, glycosylated kringle 1-3 fragment of plasminogen. *See*, for example, *Cao* (see p. 672, first column). Applicants tested antiangiogenic properties of their novel composition in an endothelial cell proliferation assay. Endothelial cell proliferation assay is considered by those of ordinary skill in the art

to provide a reasonable correlation with a condition of suppression of angiogenesis for the purpose of assessing antiangiogenic properties of a compound, such as kringle fragments of plasminogen. *See*, for example, U.S. Patent No. 5,837,682, columns 4647 (Exhibit A). Therefore, the specification provides experimental evidence that, when assessed according to a method accepted by those of ordinary skill in the art, and in comparison with the control compound possessing antiangiogenic activity, applicants' novel composition is antiangiogenic, more so than the control. Thus, the specification provides sufficient evidence that the claimed composition is antiangiogenic.

In view of the foregoing, applicants respectfully assert that the disclosure of the present application is enabling and contains working examples commensurate in scope with the claims. The specification provides sufficient guidance to a skilled artisan to make and use the claimed invention without undue amount of experimentation. Applicant respectfully requests that the rejection of Claims 1, 4, 6-12, 15 and 16 under 35 U.S.C. § 112, first paragraph, be withdrawn.

*Claim Rejections under 35 U.S.C. §112, second paragraph*

The Examiner rejects Claims 1-4, 6-12, 15, 16 and 27 under 35 U.S.C. §112, second paragraph, as indefinite.

Claim 1

The Examiner asserts the Claim 1 is indefinite because it recites the term "optionally." The Examiner states that it is not clear if "the naturally glycosylated kringle 1-3 region fragment of plasminogen is present or not." Applicants amend Claim 1 to delete the language "optionally, a protein consisting of a naturally glycosylated kringle 1-3 region fragment of a plasminogen protein." Applicants add new Claim 29. Claim 29 does not contain any new matter, and is based on Claim 1 as pending prior to the present amendment. Claim 29 is a dependent claim of Claim 1 and recites and additional element, "a protein

consisting of a naturally glycosylated kringle 1-3 region fragment of a plasminogen protein." Applicants request favorable consideration of Claim 29 and further dependent Claims 30-38.

Claim 4

The Examiner asserts that Claim 4 is vague and indefinite because it recites "the deglycosylated kringle 1-3 region fragment ... corresponding to the N-glycosylation site of human plasminogen." The Examiner asserts that it is not clear if the corresponding protein is similar or equivalent to the deglycosylated kringle 1-3 fragment of the plasminogen protein. Applicants respectfully traverse the rejection.

Applicants respectfully bring to the Examiner's attention that Claim 4 recites:

> The composition of claim 1, wherein the deglycosylated kringle 1-3 region fragment lacks a carbohydrate chain at amino acid position corresponding to the N-glycosylation site of human plasminogen.

The term "corresponding" in Claim 4 unequivocally refers to the N-glycosylation site, and not to protein. One of ordinary skill in the art would know where in the N-glycosylation site is located in the sequence of the kringle 1-3 region fragment. Therefore, the metes and bounds of Claim 4 would be clear to one of ordinary skill in the art.

In view of the foregoing, applicants respectfully assert that Claims 1, as pending upon the present amendment, and Claim 4 are definite. Applicants request withdrawal of the rejection of Claims 1-4, 6-12, 15, 16 and 27 under 35 U.S.C. §112, second paragraph.

*Rejection of Claim 27 under 35 U.S.C. §102(e)*

The Examiner rejects Claim 27 under 35 U.S.C. §102(e) as anticipated by U.S. Patent Application Publication No. 2003/0012792 (hereinafter "the cited publication"), published January 16, 2003. The Examiner previously found Claim 27 allowable. *See* Office Action mailed May 13, 2003. Now, the Examiner asserts that SEQ ID NO:2 recited in

Claim 27 is anticipated by SEQ ID NO:61 in the cited publication. Applicants respectfully traverse the rejection of Claim 27.

Applicants respectfully assert that the cited publication is not prior art with respect to the present application because the relevant part of the disclosure of the cited publication has an effective priority date that is later than the filing date of the present application.

The cited publication is a publication of U.S. Patent Application Serial No. 10/131,241 to Holaday *et al.*, filed April 25, 2002, now abandoned. It is a continuation-in-part application with the earliest priority date of May 22, 1998. The parent application No. 09/907,402, filed July 17, 2001, now U.S. Patent No. 6,554,947, was filed on July 17, 2001 (Exhibit B). **The disclosure of the parent application does not contain SEQ ID NO:61**. Thus, the effective priority date for SEQ ID NO:61 is **April 25, 2002**, the filing date of the Holaday *et al.* application. The filing date of the present application is **February 10, 2000**. Therefore, the relevant part of the cited publication is not prior art with respect to the present case.

In view of the foregoing, applicants request the Examiner to remove U.S. Patent Application Publication No. 2003/0012792 as prior art. Applicants request withdrawal of the rejection of Claim 27 under 35 U.S.C. §102(e).

## CONCLUSION

The foregoing is submitted as a full and complete response to the non-final Office Action mailed February 11, 2005. Applicants assert that the claims are now in condition for allowance and respectfully request that the application be passed to issuance. If the Examiner believes that any informalities remain in the case which may be corrected by Examiner's amendment, or that there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned agent at (404) 815-6102 is respectfully solicited.

No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies which may be required or credit any overpayment to Deposit Account Number 11-0855.

Respectfully submitted,

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